40-Hz ASSR depth of anaesthesia index

Sahar Javaher Haghighi, Dimitrios Hatzinakos
Department of Electrical and Computer Engineering, University of Toronto
{sahar,dimitris}@ece.utoronto.ca

***Abstract*—A novel method for defining an index based on multi-level clustering of 40-Hz auditory steady state response is presented in this paper. The index is a measure of depth of anaesthesia which can help monitoring depth of anaesthesia more closely and accurately. Multi-level expectation maximization (EM) is used for clustering the recorded 40-Hz auditory steady state response signals recorded from human subjects. The clustering information is used to define the depth of anaesthesia index. Rather than extracting the maximum amplitude and frequency at each cycle as clustering features, principal components analysis (PCA) is used for analyzing all samples of the cycles and projecting data into a lower dimension space. Both dimension reduction and clustering schemes are unsupervised methods, hence the algorithm does not need initial data labeling or training phase.**

I. Introduction

During surgical operations depth of anaesthesia (DoA) is constantly controlled and the does of the anaesthetic agents are adjusted by anaesthesiologists to maintain the patients in the suitable DoA . Although the clinical methods for measuring DoA are simple to be used, they are subjective and can not monitor all different stages of anaesthesia. A standard index that shows different levels in DoA will increase accuracy in monitoring depth of anaesthesia and will be a big step towards automating the process.

Investigating the effects of level of consciousness on 40-Hz auditory steady state response (ASSR) started in early nineties [1], [2], [3]. However all studies are focused on investigating the variations of two specific features in different levels of consciousness namely the maximum amplitude and phase at each ASSR cycle; some examples are [4], [5], [6], [7], [8]. In this paper we proposed an algorithm that defines an index for measuring DoA based on analyzing all samples of the ASSR cycles. The algorithm uses principal component analysis (PCA) to extract the most significant features. The low dimension samples are used for clustering the cycles into 15 clusters with a multi-level expectation maximization (EM) clustering method. DoA index, I_{DoA}, is defined based on the clustering results such that $0 < I_{DoA} < 100$ where $I_{DoA} = 100$ shows full consciousness and $I_{DoA} = 0$ shows no brain activity.

A. Background

Current cerebral monitors of DoA are either EEG or AEP based. After description of 40-Hz ASSR signals by Galombos [9] some groups started to study 40-Hz ASSR variations during anaesthesia and sleep. 40-Hz ASSR is the electrical changes in the ear and brain of a normally hearing person in response to a periodic acoustic stimuli with 40 cycles per second repetition rate. 40-Hz ASSR signal shows how neural information propagates from the acoustic nerves in the ear to the cortex [10]. 40-Hz ASSR is very sensitive to the state of consciousness. Plourde and his colleges suggested that the amplitude of the ASSR provides a more reliable indicator of the level of consciousness than EEG. They claimed that the muscle artifacts that are prominent during emergence and recovery distort EEG measurements [1]. It is observed that during Enflourane-N_2O anaesthesia 40-Hz ASSR attenuates much more sever than what one would predict from the effect of Enflourane-N_2O on AEP [11]. This renders 40-Hz ASSR more reliable than other two cerebral monitors of DoA.

In our database the Bispectral index (BIS) and MAC are also recorded at the same time with ASSR as control values. Bispectral index (BIS) (Aspect Medical System, Newton, MA, USA) is the most common EEG based depth of anaesthesia monitor. BIS is a dimensionless index between 0 and 100, where $40 < BIS < 60$ indicates the surgical level anaesthesia [12], [13]. MAC is the minimum concentration of the volatile drug vapor in the lungs that prevents movement in 50% of the subjects. MAC is widely used by anaesthesiologist as a measure of the DoA with inhalational anaesthetics.

II. Method

A. Data acquisition

After ethics approval from University of Toronto and "Research Ethics Board" of Trillium Health Partners (where the surgical procedures were conducted) 40-Hz ASSR signals were recorded from 20 human subjects. All subjects were volunteer participants over 18 years old, with no history of hear-

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ing loos or neurological problems. They have been scheduled for surgical operation for primary reasons independent of our study before being recruited.
40-Hz ASSR signals recoded from 3 to 5 minutes before injection of anaesthetic agent till emergence from anaesthesia. Clinical methods such as response to verbal and tactile stimulus as well as minimum alveolar concentration (MAC) of the anaesthetic drugs and BIS index are also recorded as control values.
Propofol which is an intravenous anaesthetic agent is used for induction of anaesthesia in all subjects and volatile anesthetic Sevoflurane is used for maintaining anaesthesia on the appropriate level during operation.
The auditory stimuli were generated with Vivosonic Integrity™ V500 as an AM-ASSR stimulus with the modulation frequency of 40.68 Hz as carrier and center frequency near 2 KHz. The stimuli was presented binaurally to the ears of the subjects by ER-3A-ABR insert earphone (Etymotic Research) at the level of 60 dB HL, loud enough to generate an ASSR but not too loud to cause discomfort for the study participants. No earmuffs were used during the recording for cancelling the auditory noise. EEG signals were recorded from 11 electrodes (F_z, C_z, C_3, C_4, T_3, T_4, A_1, A_2, O_z, $Nape$, $Forehead$), located on the skull and forehead of the subjects according to the international 10-20 electrode sites. Nicolet™ Wireless 32 amplifier is used to record the signals in 8 differential channels (T_3F_z, $T_4 - F_z$, $C_zA_1A_2$, $C_3A_1A_2$, $C_4A_1A_2$, $F_zA_1A_2$, O_zF_z, $NapeF_z$) the stimuli is also recorded with the amplifier. The sampling frequency was $12\ KHz$ and non of the electrodes had impedance above $10\ K\Omega$.

B. Data preprocessing

The signal recorded by EEG amplifier is a mixture of EEG signal, the 40-Hz ASSR and noise. The ASSR signal ratio in the recorded data is very low since amplitude of the ASSR signal is about one tenth of the background EEG. ASSR is buried in EEG signals hence the first step is to denoise and extract the ASSR from the background noise and EEG signal.
In the preprocessign stage the signals are downsampled five times and the outlier samples are removed. Assuming the data is normally distributed the samples further than $3 \times SD$ from the mean value are considered to be outliers. The signals are then filtered with butterworth filters to filter out the frequencies outside the frequency range 35 Hz $\leq f \leq 45$ Hz and 75 Hz $\leq f \leq 85$ Hz. The filtered signals from the eight amplifier channels are then synchronized with the stimuli cycles recorded with amplifier on the ninth channel. The duration of the signal synchronized with each stimuli sweep is called an epoch. Each epoch is modeled as:

$$x_k[l] = s_k[l] + r_k[l] \tag{1}$$

where $x_k[l]$ is the ASSR synchronized with the k_{th} sweep of the stimuli and $r_k[l]$ is the EEG and noise from the other sources.

For extracting the signal we used ensemble averaging. Weighted ensemble averaging over 300 ASSR epochs is used for extracting each ASSR cycle (Eq. 2). The weights are inversely proportional to the variance of noise (Eq. 2).

$$\begin{aligned} \hat{x}[l] &= \frac{1}{K}\sum_{k=1}^{K}\omega_k x_k[l] \\ \omega_k &= \frac{\alpha}{E(x_k - E(x_k))^2} \end{aligned}$$

Under the assumption that $s_k[l]$ is phase locked to the stimuli, noise $r_l[l]$ is zero mean, $E(r_l[l]) = 0$, has constant variance, $var(r_k) = \sigma^2$ and is uncorrelated from one sweep to another, $E(r_l[l]r_k[l-m]) = \rho_r[m]\delta(l-m)$ the estimator is unbiased and decrease the variance of the noise. More details on extracting 40-Hz ASSR cycles can be found in [7], [8].

C. Algorithm

After ASSR cycles were extracted, principal component analysis (PCA) is used to extract the dominant features. PCA projects data from a d-dimensional space on to a k-dimensional space, where $k < d$ such that the samples have the highest possible variance after being projected on W [14].

$$y = W^T x$$

Here x is the array of samples in d-dimensional space and y is the extracted features in the k-dimensional space, where $k < d$. W is the matrix of the first k eigenvectors of $S = cov(X)$, sorted according to the size of eigenvalues. Knowing that the the average of eigenvalues is equal to the average variance of the signal,

$$\sum_i \lambda_i = \sum_i s_i$$

where s_i is the i_{th} element of the covariance matrix, the number of projected features can be chosen such that the desired portion of the data variance preserves. The percentage of the variance preserved by the k principle components as defined in equation 2 [15].

$$\frac{\lambda_1 + \lambda_2 + \lambda_3 + \cdots + \lambda_k}{\lambda_1 + \lambda_2 + \lambda_3 + \cdots + \lambda_k + \cdots + \lambda_d} \times 100. \tag{2}$$

It is assumed for clustering that the data has Gaussian mixture density. A mixture density is modeled as

$$p(y) = \sum_{i=1}^{c} p(y|G_i)P(G_i) \tag{3}$$

where c is the number of components G_i in the mixture, $p(y|G_i)$ is the component density and $P(G_i)$ is the mixture proportion. Since the components are multivariate Gaussian the components' densities are $\mathcal{N}(\mu_i, \Sigma_i)$ and $\Phi = \{P(G_i), \mu_i, \Sigma_i\}_{i=1}^{c}$ are the parameters to be estimated. In clustering with EM each Gaussian component corresponds to a class and we look for the component density parameters that maximize likelihood of the samples.

$$\begin{aligned} \mathcal{L}(\Phi|Y) &= \log \prod_t p(y^t|\Phi) \\ &= \sum_t \log \sum_{i=1}^{c} p(y^t|G_i)P(G_i) \end{aligned} \tag{4}$$

The equation (Eq. 4) is not analytically solvable; EM algorithm [16], [17] is used to iteratively maximize likelihood. In the EM algorithm a hidden variable z is defined and the likelihood of the joint distribution of y and z, $\mathcal{L}(\Phi|y,z)$, is maximized. Since z is not observed the expectation of likelihood is calculated. In each iteration on the expectation phase samples are clustered assuming the mixture model Φ_l and expected likelihood are calculated. On the maximization phase Φ_{l+1} will be calculated such that it maximize the expectation. Φ_{l+1} will be used at the next iteration for clustering the samples (expectation phase).

$$\begin{aligned} \mathcal{Q}(\Phi|\Phi^l) &= E[\mathcal{L}(\Phi|Y,Z)|Y,\Phi^l] \\ \Phi^{l+1} &= \arg\max_{\Phi} \mathcal{Q}(\Phi|\Phi^l) \end{aligned}$$

Is it proven that increasing the likelihood of joint distribution $\mathcal{L}(\Phi|Y,Z)$ will increase likelihood of distribution of Y $\mathcal{L}(\Phi|Y)$ too [16], [15].
Assuming that the features can be modeled with Gaussian Mixture Model, at the fist clustering level the signals have been clustered into 2 main Gaussian components that splits data into conscious (C cluster) and anaesthetized (A cluster). On the next level C clustered data will be clustered into 5 and A clustered data into 10 clusters.
Once the samples are clustered in two levels data labels and the posterior probability of each sample will be used for defining the depth of anaesthesia index I_{DoA}. The clusters will be sorted and labeled according to the euclidian distance of their mean value from each other after clustering. The ones with closer mean values will be labeled with consecutive numbers as labels. These labels are filtered with a moving average filter where the filter coefficients are the product of a neighboring factor and the clustering posterior probability of samples to compute the DoA index.

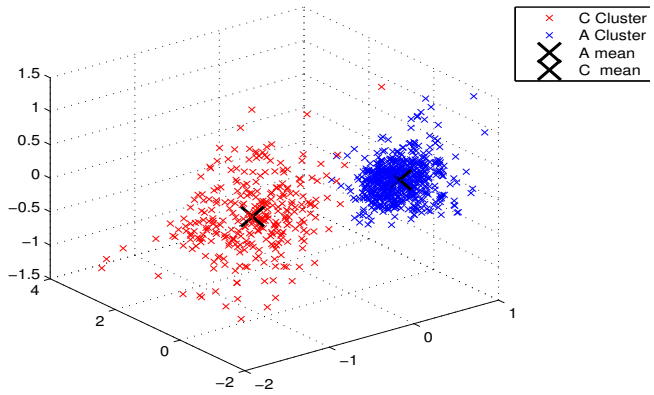

Fig. 1: Clustered data after first level clustering of $C_4 - A_1A_2$ channel of subject 3 ASSR with three dimensional data points.

$$\begin{aligned} I &= L \times \omega^T \\ L &= [l^{t-n} \dots l^t \dots l^{t+n}] \end{aligned} \tag{5}$$

$$\begin{aligned} \omega = [(1/2)^{|-n|} p(y^{t-n}|G^{t-n}) \cdots p(y^t|G^t) \cdots \\ (1/2)^{|n|} p(y^{t+n}|G^{t+n})] \end{aligned} \tag{6}$$

Here n is the number of neighbor samples on each side, L is the vector of labels. n is chosen as 4 and L varies between 1 to 15. Finally the index I is scaled to $0 < I_{DoA} < 100$.

III. Results

The multi-clustering algorithm is applied to the recorded 40-Hz ASSR signals. PCA is applied to data samples to extract the first k features that contain 75% of data energy. k varies between 2 and 6 in different channels and for different subjects. On the first level clustering EM is done with 500 iterations. The algorithm is repeated 10 times, each time with a new set of random initial component parameters and the one with largest likelihood is chosen. The fist level of clustering divides the data into conscious (C cluster) and anesthetized (A cluster) cycles. Figure 1 shows the clustered data for an ASSR signal in which the dimension number is reduced to 3.

Figures 2 and 3 show how the cycles are labeled in time relative to the clinical markers in two subjects in channel $T_3 - F_z$ and $C_4 - A_1A_2$ respectively. The markers are times of the injection of Fentanyl, Propofol and loosing eyelash reflex on the induction

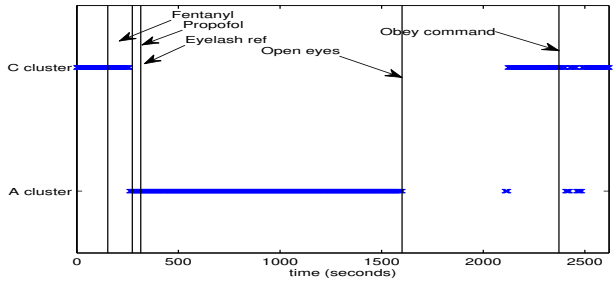

Fig. 2: First level clustering labels for $C_4 - A_1A_2$ channel of subject 3 ASSR. The labels are presented on each cycle time. The clinical markers are presented with vertical lines.

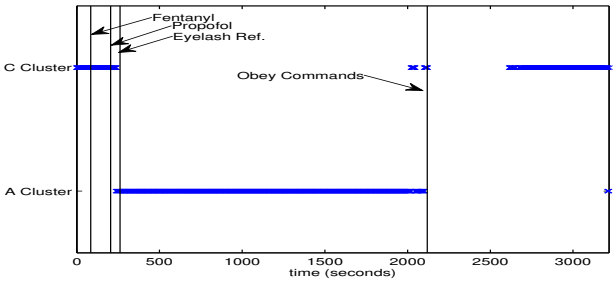

Fig. 3: First level clustering labels for $T_3 - F_z$ channel of subject 10 ASSR. The labels are presented on each cycle time. The clinical markers are presented with vertical lines.

side and time of opening eyes and, obeying command on the emerging side. The patient is fully anaesthetized once his/her eye lash reflex disappears. Emerging from anaesthesia, patients usually open their eyes first but they will not be considered fully conscious before being able to obey commands. It can be seen in figures 2 and 3 that most of the cycles are labeled as 'A' after the eyelash reflex marker, and most of the cycles are labeled as 'C' after obeying command. In both signals there is a small gap after opening the eyes when data is not recorded while the patients were transferred from the operation room to the recovery room. Subject 10 opened his eyes at the same time he obeyed the commands.

On the second level of clustering the 'C' clustered data samples are clustered to 5 clusters and the 'A' clustered data samples into 10. Similar to the first level, clustering is done in 500 iterations and 10 repetitions with random initial component parameters. Figures 4 and 5 show the DoA index on $T_3 - F_z$ channel of subject 3 and $C_4 - A_1A_2$ channel of subject 10 together with the BIS and MAC values recorded at the same time. In each figure the top

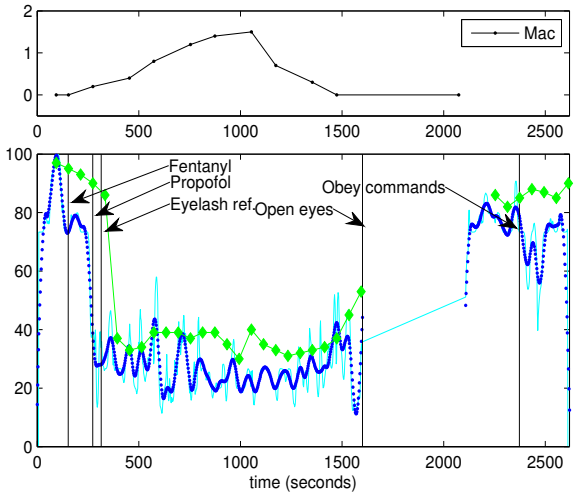

Fig. 4: DoA index for subject 3 on $C_4 - A_1A_2$ channel over the time. Top plot shows MAC values. On the bottom plot the green line with diamonds is the BIS index, the cyan solid line is the I_{DoA} and the blue dots are the smoothed I_DoA. The clinical markers are presented with vertical lines.

plot shows MAC variations. On the bottom plots the solid cyan lines are the DoA index values and the blue dots are the smoothed DoA index. It can be seen that the MAC, BIS and DoA index variations are consistent in time. The patients have the lowest DoA index while MAC is at its highest values. The index is above 60 when the patient is conscious and starts decreasing after the injection of anaesthetic agents. The index is below 50 when patients are on the surgical level of anaesthesia. On the emergence from anaesthesia the index rises back to above 50. In figure 5 some of BIS values are missed (between seconds 1000_th and 1500_th) that is because the noise level from other equipments in the room was very high during those seconds and the BIS monitor could not evaluate the index.

IV. Conclusion

An unsupervised method for defining depth of anaesthesia index is proposed in this paper. The algorithm defines the DoA index based on clustering information of 40-ASSR signals. DoA index varies between 100 and 0, where 100 shows full consciousness and 0 shows no brain activity.
The defined index variations is consistent with the control values namely MAC and BIS. DoA index will help anaesthesiologist to monitor different depths of anaesthesia more closely and is a big step towards automation of anaesthesia monitoring.

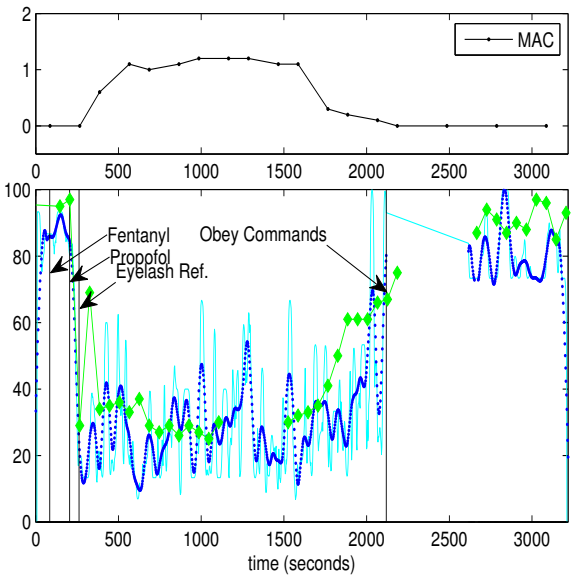

Fig. 5: DoA index for subject 10 on $T_3 - F_z$ channel over the time. Top plot shows MAC values. On the bottom plot the green line with diamonds is the BIS index, the cyan solid line is the I_{DoA} index and the blue dots are the smoothed I_{DoA} index. The clinical markers are presented with vertical lines.

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